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ENDOCRINE GLANDSV. THE ISOLATED HEART AS AN INDICATOR OF ADRENAL SECRETION
INDUCED BY PAIN, ASPHYXIA AND EXCITEMENT

BY

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Knowledge of the conditions under which the endocrine glands become active or manifest increased activity is important for several reasons. Such knowledge is valuable as an extension of our acquaintance with a realm of physiology which is still largely unexplored. It permits correlated studies of other bodily processes which vary under the same conditions. And it gives a basis for inquiry into the functions performed by the endocrine glands, for the service of an organ should reasonably be looked for in relation to the times of its special activity. With such ideas in mind, the present series of studies was entered upon.

In two papers published in 1911, Cannon, in collaboration with de la Paz (1) and with Hoskins (2), brought forward evidence that the adrenal medulla was stimulated to secrete by emotional excitement, by "pain" and by asphyxia. Adrenal secretion had previously been proved to be subject to sympathetic stimulation by way of the splanchnics; and as excitement, pain and asphyxia were conditions well recognized as accompanied by sympathetic activity (manifested, e.g., by inhibition of digestive functions), an attendant adrenal secretion was naturally to be expected. In a series of papers which followed these first two, experiments were described showing that adrenal secretion was serviceable in lessening muscular fatigue (3) and in accelerating coagulation of the blood (4). An interpretative paper (5) pointed out that excitement, pain and asphyxia were conditions which in natural existence would commonly be associated with struggle, and that the visceral changes, including adrenal secretion, which accompany these three states, would be useful in great muscular effort. This interpretation presented a new view of the function of the sympa-

thetic division of the autonomic system and of the adrenal medulla in important bodily adjustments.

Within the past few years both the evidence on which the foregoing interpretation was based and the interpretation itself have been seriously questioned. In an extensive series of papers, Stewart and Rogoff have reported apparently careful quantitative studies on the rate of adrenal discharge, and have drawn the conclusions that the discharge is continuous, that in any animal it is approximately constant, and that the supposed variation is dependent on the rate at which the blood flows through the lumbo-adrenal veins (6). They found no increase of secretion in pain (7), asphyxia (8) or emotional excitement (9). More recently Gley and Quinquaud have also examined experimentally adrenal secretion and have come to the decision that adrenin is not secreted in sufficient amount to be carried effectively to the organs on which it may act, and that therefore no true physiological adrenalinemia exists (10). The sharp difference between the views put forth by Cannon and his coworkers and the ideas supported by these later investigators warrants a reëxamination and a thorough testing of the evidence for adrenal secretion in pain, asphyxia and excitement.

REVIEW OF THE POSITIVE EVIDENCE

1. *That adrenal secretion is induced by sensory stimulation.* In the original tests Cannon and Hoskins (2) made use of rhythmically contracting segments of rabbit intestine suspended lengthwise in a glass cylinder through which oxygen was passed. The segment, when not surrounded by the blood to be tested, was bathed in Ringer's solution. The test blood, the cylinder and the fresh Ringer's solution were all kept at body temperature in a common bath. The blood to be tested was taken before and after the experimental procedures by passing a catheter through a nick in the femoral vein into the iliac and thence into the inferior vena cava anterior to the entrance of the lumbo-adrenal veins. A thread tied tightly around the catheter marked the point to which it was inserted and permitted reinsertion to the same point in subsequent sampling of the blood. The position of the catheter opening, which was at one side, was kept constant by attention to the position of the knot in the thread. Thus both the control blood and the blood after stimulation were taken as exactly as possible from the same region. Under these circumstances normal blood removed before stimulation of the central end of the sciatic nerve caused no inhibition

of the rhythmically contracting intestinal segment, whereas that removed afterwards produced a marked relaxation. The conclusion was drawn that the adrenal glands are affected through nervous channels when a sensory trunk is strongly excited and that they then pour into the blood stream their secretion.

The foregoing conclusion was supported a year later (1912) by Anrep who found that the denervated limb or kidney at first expands but later quickly contracts when the central end of the cut sciatic nerve is stimulated (11). If the adrenal glands were removed or the splanchnic nerves were cut, the phase of contraction disappeared. Since the organs (limb or kidney) were denervated, the only factor which could cause their contraction in the presence of a rise of general blood pressure must be some agency brought by the blood stream; and since the phenomenon disappeared on exclusion of the adrenals, the conclusion was drawn that adrenal secretion, poured out in consequence of reflex stimulation through the splanchnics, produced the observed vasoconstriction.¹ The observations of Anrep on the denervated limb have recently been confirmed by Pearlman and Vincent (12).

The following year (1913) Levy reported the incidental observation that after both stellate ganglia had been removed and both vagus nerves cut, stimulation of the sciatic nerve occasioned irregularity of the heart (13). He also noted that excitation of the peripheral end of the cut splanchnic would cause the same cardiac changes, and that they did not occur if the adrenal gland was removed on the stimulated side. He therefore concluded that on sciatic stimulation the denervated heart was being affected by adrenin discharged reflexly.

In 1917 Florovsky (14) undertook an investigation of a strange fact previously observed by Ostrogorsky, which was that if the cervical sympathetic and the chorda tympani nerves are severed, and the secretory effect of a dose of pilocarpin is disappearing, sciatic stimulation causes a considerable increase in the flow of saliva. The effect was so striking that he looked for a third nerve to the submaxillary gland but could not find it. Under the conditions described by Ostrogorsky, Florovsky succeeded in producing augmented salivary secretion

¹ In the same year with Anrep's observation, Elliott reported (*Journ. Physiol.*, 1912, xliv, 406) exhaustion of the adrenal gland with intact nerve supply when the sciatic nerve was stimulated periodically for four hours. Since Elliott's methods were concerned with a quantitative assay of the amount of adrenin left in the gland after stimulation, and not directly with adrenal secretion, his results will not be considered in the present review of the evidence.

by stimulating the peripheral end of the cut splanchnic and by intravenous injection of adrenin. He also confirmed Ostrogorsky's observation of an augmented flow after sciatic stimulation. This reflex secretion did not occur, however, if both adrenal glands were extirpated, or if one was extirpated and the vein of the other obstructed, or if both splanchnic nerves were cut. He concluded, therefore, that the anomalous secretion from the denervated submaxillary gland is due to adrenal secretion resulting from reflex stimulation.

The foregoing evidence, involving tests made on blood removed from the body, and tests made in the body on the denervated limb, the denervated kidney, the denervated salivary gland and the denervated heart, are harmonious in testifying to a reflex discharge of the adrenal glands when a sensory nerve is stimulated.

2. *That adrenal secretion is induced by asphyxia.* In their examination of the effect of asphyxia on adrenal secretion, Cannon and Hoskins (2), in 1911, used the same methods that were employed for testing the effect of sensory stimulation. In the course of the examination it was discovered that *extreme* asphyxia would cause a change in the blood which would produce the same effect as adrenin on the beating intestinal strip, i.e., inhibition, and this even though the adrenal glands were carefully removed or the circulation confined to the region above the diaphragm. This observation indicated the necessity for careful control at the time the asphyxial blood was taken. Accordingly, after *moderate* asphyxia, there was removed from the femoral vein blood which should serve as a control sample of the systemic venous flow below the entrance of the lumbo-adrenal veins; and at as nearly as possible the same time another sample was removed from the inferior vena cava at a point anterior to the opening of these veins. This latter blood caused the typical inhibition indicating the presence of adrenal secretion, whereas the control femoral blood, like the vena cava blood taken before asphyxia, failed to cause inhibition. Through the use of the control, therefore, the presence of an accessory factor, simulating the action of adrenin, was ruled out. Consequently the conclusion was drawn that asphyxia results in secretion of the adrenal glands.²

² At about the same time that the paper by Cannon and Hoskins was published, Starkenstein (Zeitschr. Exper. Path. Therap., 1911, x, 78) reported that in one rabbit asphyxia caused nearly an abolition of the color reaction of the adrenal gland connected with the central nervous system, whereas the other gland, with its nerve severed, showed a good color reaction. In 1912, Borberg (Scand. Arch.

In 1912 Anrep (11) noted that a decrease in volume of the denervated limb and denervated kidney occurred during asphyxia, in spite of a general rise of arterial pressure, just as he had seen it occurring as a consequence of sciatic stimulation. This vascular constriction appeared, however, only when the adrenal glands were connected with the circulation and the splanchnic nerves were intact. When the adrenal glands were out of circulation, asphyxia caused some rise of arterial pressure, though less than in the intact animal, but no constriction in the vessels of the denervated limb or kidney. He concluded, therefore, that the adrenal glands are excited during asphyxia. These observations of Anrep on the constriction of the vessels in the denervated limb were at once confirmed by Itami (15), who found that it did not occur after transection of the cord. Since the constriction was not due to the direct action of CO_2 on the vessel wall, nor to reaction of the vessels to an increased internal pressure, he interpreted the result as due to increased adrenal secretion.

In 1914 Gasser and Meek, while making observations on a dog with stellate ganglia removed and the vagi cut, noted, when the animal was asphyxiated for 30 seconds, an acceleration of the heart beat amounting to 92 beats per minute (16). Now, under ether anesthesia, the blood vessels of the adrenal glands were tied. After recovery from the operation, asphyxia lasting 90 seconds caused an acceleration of only 8 beats per minute.

In 1917 Gley and Quinquaud found an amount of adrenin in adrenal venous blood obtained during asphyxia considerably in excess of that obtained when the animal was undisturbed (17). Using the rise of blood pressure as a test, they determined that from 4 to 8 cc. of the asphyxial adrenal blood were equivalent to 16 cc. of the blood before asphyxiation. In their experiments injection of 20 cc. of blood from the inferior vena cava, taken above the adrenal veins after 3 or 4 minutes of asphyxia, caused a rise of arterial pressure from 24 to 45 mm.

Physiol., xxviii, 124) quoted Fridericia as having performed six experiments on guinea pigs poisoned with an excess of CO_2 with some diminution of the chrome reaction in the glands. In the same year, Kahn (Arch. f. d. gesammte. Physiol., 1912, cxlvi, 578) reported asphyxia in monkeys as causing a marked difference in the adrenin content of the two adrenal glands, one of which was removed before asphyxia, the other afterwards. The adrenin present was quantitated by the use of Laewen's preparation. Since these observations, although they support the view that asphyxia causes adrenal secretion, are really assays of the amount of adrenin left in the gland after asphyxia, and do not give direct indication of adrenal activity, they will not be further considered in the present paper.

higher than that produced by injecting an equal quantity of cava blood taken from the same level before asphyxia.³

The foregoing evidence which, like that obtained after sensory stimulation, was the result of studies by various observers using a variety of methods, is harmonious in leading to the conclusion that adrenal secretion is increased by the asphyxial state.

3. That adrenal secretion is induced by excitement. In the experiments on the influence of emotional excitement, performed by Cannon and de la Paz in 1911 (1), the methods employed were similar to those used by Cannon and Hoskins. The only differences were that the animals did not receive a general anesthetic and that the catheter was introduced under local anesthesia. Controls were obtained in every instance. As the original records show, after emotional excitement the blood drawn from the inferior vena cava anterior to the opening of the adrenal veins repeatedly caused inhibition of the beating intestinal strip, whereas that removed before excitement had no such effect. Since excitement after removal of the adrenal glands did not yield this result, and since the effective blood lost its inhibitory power when exposed to oxygen (a procedure known to destroy adrenin), the inference was drawn that adrenal secretion is stimulated by great emotion.

These conclusions were confirmed in 1913 by Hitchings, Sloan and Austin (18), who used the same method to obtain blood and the same test for adrenin that Cannon and de la Paz had used. They found that after great fear and rage had been induced in a cat by the attempt of a muzzled dog to fight it, the adrenin reaction was clearly demonstrable. The reaction did not occur, however, if the splanchnic nerves had been previously severed.

In 1918 Redfield reported that in the horned toad nervous excitement causes a contraction of the melanophores in the denervated skin, a reaction which does not occur after the removal of the adrenal glands (19).

In addition to these direct observations on the stimulating effect of strong emotion on adrenal secretion, there were other observations having inferential value. In 1914 Cannon and Mendenhall, after show-

³ Gley and Quinquaud express the opinion that the experiments of Cannon and Hoskins were indecisive in determining the effect of asphyxia on adrenal secretion, because relaxation of the intestinal strip could be induced by blood removed from the asphyxiated animal after the adrenals had been excised. They seem not to have paid attention to the control observations which Cannon and Hoskins were careful to make (see p. 402).

ing that clotting of the blood is hastened by stimulation of the splanchnic nerves, found that great excitement will cause the same effect (4). The evidence which they brought that injected adrenalin shortens the clotting time, that when the splanchnic nerves are stimulated the adrenal glands are necessary for the effect, and that excitement induces faster clotting only so long as the splanchnic nerves are intact, was confirmatory of the view that excitement causes adrenal discharge.

In 1915 Lamson noted that injection of adrenalin would cause a polycythemia, and that emotional excitement, such as fear and rage, would likewise cause it (20). If an animal was frightened after removal of the adrenal glands, however, there was no increase in the red count. Lamson observed that asphyxia had the same effect as fright and that removal of the adrenals prevented the customary increase seen after asphyxiation.

By both direct and indirect testimony, offered by different observers using different methods, the evidence is concordant that emotional excitement is accompanied by increased secretion of the adrenal medulla.

All of the observations cited above, leading to the conclusion that adrenal secretion is increased in pain, asphyxia and excitement, were on record before the negative results of recent investigations were published. These positive data have all been consistent, they were obtained by a number of quite independent workers, and they were the outcome of a variety of operative procedures each differing from those yielding the negative results. In view of these facts it would appear that this body of cumulative testimony deserved more consideration than it received, and warranted a comparison of experimental methods.

A CONSIDERATION OF CRITICISMS OF THE CATHETER METHOD

In criticism of the catheter method used by Cannon and Hoskins, Stewart and Rogoff declare first, that the results obtained by it are valid only if the blood flow is assumed to be constant during the whole experimental period; and second, that the method does not permit any judgment on this point (7). Thus, if there be a continuous secretion of adrenin undisturbed by reflex stimulation, as they maintain is the case, there could be an increased concentration only if the blood flow through the adrenal vessels were retarded. There is another possibility, however, which should be considered. The blood flow through the adrenal vessels might be *increased*. Strong sciatic stimu-

lation has a well-known pressor effect. This may be due largely to reflex splanchnic stimulation. But there is no evidence that splanchnic stimulation causes constriction of adrenal vessels. Indeed, the careful observations of Burton-Opitz and Edwards (21) have shown that stimulation of the splanchnic nerves causes a greater blood flow through the adrenal vein, a result which Biedl had previously noted (22). With a heightened general blood pressure and at least no constriction of the adrenal vessels, the blood flow through these vessels must necessarily be increased. Under these circumstances, on the basis of Stewart and Rogoff's argument, the adrenin would be more *dilute* rather than more concentrated in the adrenal blood. A faster flow in the inferior cava which might accompany the higher arterial pressure would still further dilute the secreted adrenin. With heightened arterial pressure, therefore, the conditions which would prevail in the inferior cava anterior to the adrenal veins would be highly unfavorable for demonstrating a greater concentration of adrenin, if adrenal secretion were constant and unvarying. The positive evidence which was obtained that adrenin is actually *concentrated* in the circulating blood at this point in times of stress indicates, definitely, an increased secretion from the glands.

The suggestion that the positive results obtained by Cannon and his collaborators might have been due to a fortunate location of the eye of the catheter (7) seems to have been made with disregard for the care exercised in making control observations under precisely the same conditions before and after stimulation.

Stewart and Rogoff's few attempts to obtain reactions from intestinal strips by use of blood taken by catheter from the inferior cava were unsuccessful (7). They explain their lack of success by supposing that the adrenal secretion was too highly diluted by cava blood. Without direct observation of their technique it is difficult to suggest the reason for their failure to obtain the positive results undoubtedly demonstrated by the catheter method. It may be stated, however, that the method is difficult and exacting, and that not until after some experience with it did it begin to yield us positive results.

THE DENERVATED HEART AS AN INDICATOR OF ADRENAL SECRETION

The difficulties encountered in testing for adrenin in blood removed from the body render desirable a simpler method which will yield reliable results in the hands of any competent experimenter. In 1917 Cannon (23), making use of the hint offered in the incidental observations of

Levy (13) and of Gasser and Meek (16), suggested the employment of the completely denervated heart to demonstrate an increase of adrenin in the circulating blood.⁴

This is a preparation which is likely to be highly serviceable in the further elucidation of adrenal function. In the first place, the preparation has important advantages dependent on testing the blood while it is still in the body—advantages which were praised by Stewart and Rogoff (7), but which were lacking in their use of the intestine and uterus as indicators. These advantages are: security against loss of adrenin in manipulation, avoidance of a development of the pressor property of clotted blood, exclusion of the possible effects on secretion of loss of blood or adrenin from the organism, and finally the possibility of direct quantitative comparison of adrenal secretion induced by successive stimulations. Further, the denervated heart is an organ highly sensitive to adrenin; intravenous injection of adrenalin at the rate of 0.001 mgm. per k. per minute has increased the heart rate as much as 28 beats per minute. Moreover, the method permits a graphic record from which may be judged the latent period and the duration of secretion of the adrenal glands in consequence of stimulation. And finally, the necessary operation (severance of the vagus nerves and removal of the stellate ganglia between the first two ribs on either side) is so simple that anyone inclined to doubt that more adrenin is secreted, in consequence of reflex or other stimulation, may readily make the test.

Sensory stimulation. In a cat under urethane, with vagi cut and stellate ganglia excised, stimulation of the central end of the cut sciatic will cause the heart rate to increase in some instances as much as 50 beats a minute.⁵ Comparisons of the increased rate due to sciatic stimulation with the effects of adrenalin (quantitated as base) injected intravenously indicate that the range of reflex adrenal secretion lies

⁴ At the same time Cannon reported (Science, May, 1917, xlv, 463) that the denervated heart revealed an increase of adrenal secretion after sciatic stimulation or asphyxiation, and promised a full report of the experiments in this Journal. Absence from the United States for nearly two years has unavoidably delayed the complete paper until this time.

⁵ Many years before Levy's observation, Hunt noted (this Journal, 1899, ii, 444) that stimulation of a sensory nerve would cause cardiac acceleration after all cardiac nerves were divided, and that the same result followed stimulating the peripheral splanchnic. It differed from the acceleration following sympathetic stimulation by beginning slowly, i.e., about ten seconds after the start of stimulation. It is interesting to observe that this period is almost exactly that required for the distribution of adrenal secretion by the circulating blood.

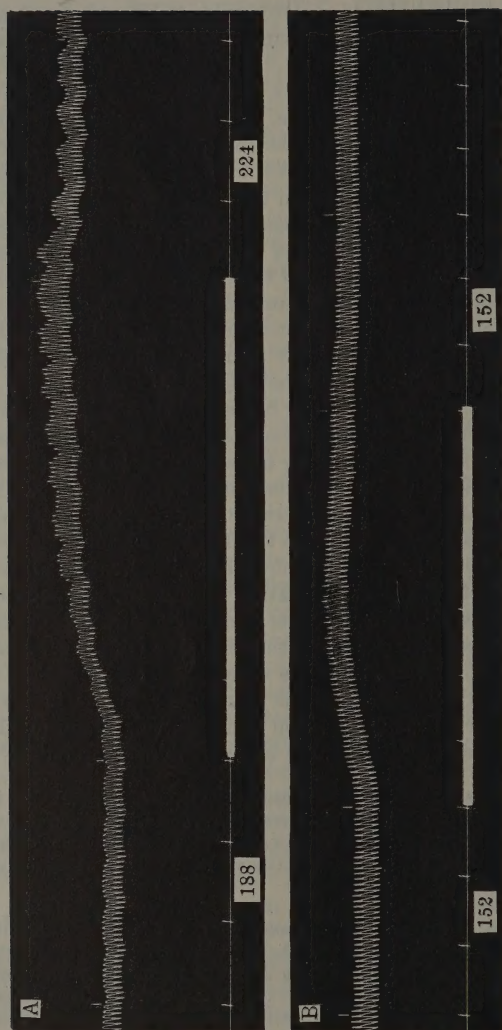


Fig. 1. Records of the beat of the denervated heart, membrane manometer. Time intervals, 5 seconds.
A, Sciatic stimulation 30 seconds, 2:21. Increase of rate from 188 to 224 per minute. (Adrenal glands tied off, 2:52).
B, Sciatic stimulation 30 seconds, 3:10. No increase of rate.

TABLE 1

Examples of increased rate of the denervated heart on sciatic stimulation

DATE	TIME	SCIATIC STIMULATION	RATE BEFORE	RATE AFTER	INCREASE PER MINUTE
March 21.....	2.58	30 seconds	220	264	44
	3.04	30 seconds	220	256	36
	3.15	15 seconds	212	240	28
	3.16	Splanchnics cut			
	3.25	30 seconds	184	192	8
	3.28	15 seconds	184	192	8
March 23.....	2.16	30 seconds	176	228	52
	2.21	30 seconds	188	224	44
	2.52	Adrenal glands tied			
	3.07	15 seconds	152	156	4
	3.10	30 seconds	152	152	0
April 6.....	2.31	30 seconds	216	240	24
	2.39	30 seconds	212	236	24
	3.12	30 seconds	184	208	24
	3.15	30 seconds	196	216	20
April 7.....	2.50	30 seconds	200	236	36
	2.52	30 seconds	200	224	24
	2.56	30 seconds	200	244	44
	3.01	30 seconds	200	240	40
	3.05	Cerebrum removed			
	3.19	30 seconds	208	236	28
April 21.....	1.01	45 seconds	144	180	36
	1.05	55 seconds	152	184	32
	1.14	55 seconds	156	180	24
	1.20	55 seconds	156	180	24
	1.33	50 seconds	162	192	30
	1.54	Right adrenal tied, left splanchnic cut			
	2.06	45 seconds	164	164	0
May 7.....	10.35	30 seconds	156	180	24
	10.43	40 seconds	156	180	24
	10.47	45 seconds	156	180	24
	11.03	Both adrenals removed, 100 cc. gum-salt solution			
	11.07	40 seconds	174	174	0
	11.10	40 seconds	138	138	0

between 0.001 and 0.005 mgm. per k. per minute—i.e., from five to twenty-five times the amount regarded by Stewart and Rogoff as the normal output. Reflex increase of the cardiac rate does not occur if the adrenal glands are removed (see fig. 1 and table 1).

Asphyxia. Asphyxiation of the cat with the heart completely denervated will cause a noteworthy increase in the heart rate (see fig. 2 and table 2), an effect not seen after adrenalectomy. The figures in table 2 illustrate another point mentioned in 1917, viz., that an indication of adrenal secretion may be obtained from the denervated gland if asphyxia is prolonged. In the experiment of February 24, for example, asphyxia for 20 seconds, though previously effective, caused no change after severance of the splanchnics. In that of February 27, asphyxia of 60 seconds caused no change after splanchnic section; and in that of February 28, though asphyxia of 35 seconds had been highly effective before the splanchnics were cut, thereafter asphyxia of 45 seconds increased the heart rate only 4 beats per minute, whereas asphyxia of 90 seconds caused an increase of 68 beats a minute. Similar differences are observed in the experiment of March 21. Unfortunately these observations were not checked by final proof that cutting the splanchnics completely denervated the glands, though the marked drop in pulse rate may be regarded as testimony to that conclusion. The results are in agreement, however, with evidence adduced by Czubalski (24) that asphyxia, if sufficiently prolonged, may have a direct stimulating action on the adrenal medulla, and perhaps on other chromaffine tissue as well.

In 1917 Cannon described another method of demonstrating adrenal secretion, which consists in cutting all the nerves in the gastro-intestinal mesentery, tying all the limb arteries and the carotids, and thus leaving the circulation confined chiefly to the splanchnic area which, however, is denervated (23). Under these circumstances it is not uncommon for asphyxia to cause a slight rise of pressure after an interval of 40 to 60 seconds and a very considerably greater rise as soon as respiration begins again; these results do not occur if the adrenal glands are excluded (see fig. 3).

Emotional excitement. The completely denervated heart can be used as an indicator of adrenal secretion in testing the influence of emotional excitement quite as well as in testing the influence of sensory stimulation and asphyxia. It is only necessary to take somewhat greater pains in order to keep animals in normal condition after operation. To denervate the heart, the stellate ganglia are first removed

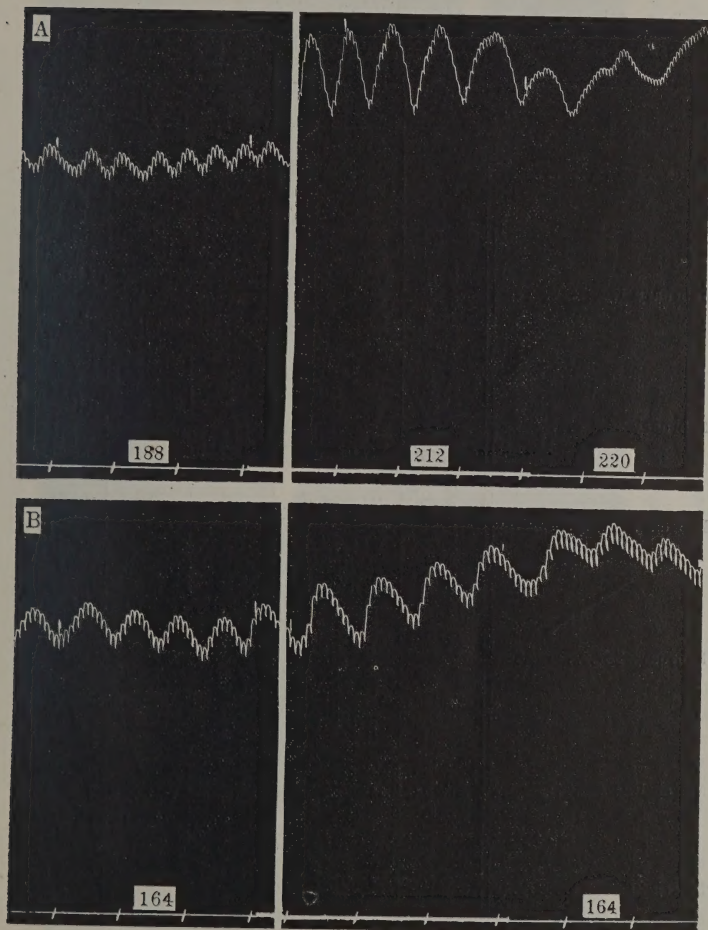


Fig. 2. Beginning and end of records of the beat of the denervated heart, mercury manometer. Original size. Time intervals, 5 seconds.

A, Asphyxia 60 seconds, 3:55. Increase of rate from 188 to 220 per minute. (Adrenal glands tied off, 4:45).

B, Asphyxia 60 seconds, 4:50. No increase of rate. Blood pressure rose from 92 to 124 mm. Hg.

TABLE 2

Examples of increased rate of the denervated heart on asphyxiation. (In the first five cases the abdomen had been opened)

DATE	TIME	ASPHYXIA	RATE BEFORE	RATE AFTER	INCREASE PER MINUTE
January 25.....	{	80 seconds	240	256	16
		Adrenals removed			
		90 seconds	192	192	0
February 17.....	{	2.50 60 seconds	162	202	40
		2.58 60 seconds	158	200	42
		3.01 Veins tied both sides of adrenal glands			
		3.04 60 seconds	166	206	40
		3.10 Adrenal glands tied off completely			
		3.18 60 seconds	146	146	0
February 24.....	{	3.35 40 seconds	204	256	52
		3.38 20 seconds	216	228	12
		4.10 Splanchnics cut in thorax			
		4.15 20 seconds	204	204	0
February 27.....	{	3.28 90 seconds	208	236	28
		3.41 Splanchnics cut in thorax			
		3.43 60 seconds	188	188	0
February 28.....	{	11.39 35 seconds	180	212	32
		12.08 Splanchnics cut in thorax			
		12.10 45 seconds	164	168	4
		12.13 90 seconds	156	224	68
		12.18 90 seconds	172	224	52
		12.25 Veins tied both sides of adrenal glands			
		12.31 90 seconds	168	180	12
March 16.....	{	2.51 60 seconds	196	212	16
		3.05 45 seconds	208	228	20
		3.59 90 seconds	188	224	36
March 21.....	{	3.09 45 seconds	220	240	20
		3.20 Splanchnics cut in thorax			
		3.30 90 seconds	180	212	32
		3.35 45 seconds	176	188	12
March 23.....	{	2.24 60 seconds	192	236	44
		2.34 Abdomen opened	192	204	12
		2.53 Adrenal glands tied off completely			
		3.20 60 seconds	152	156	4

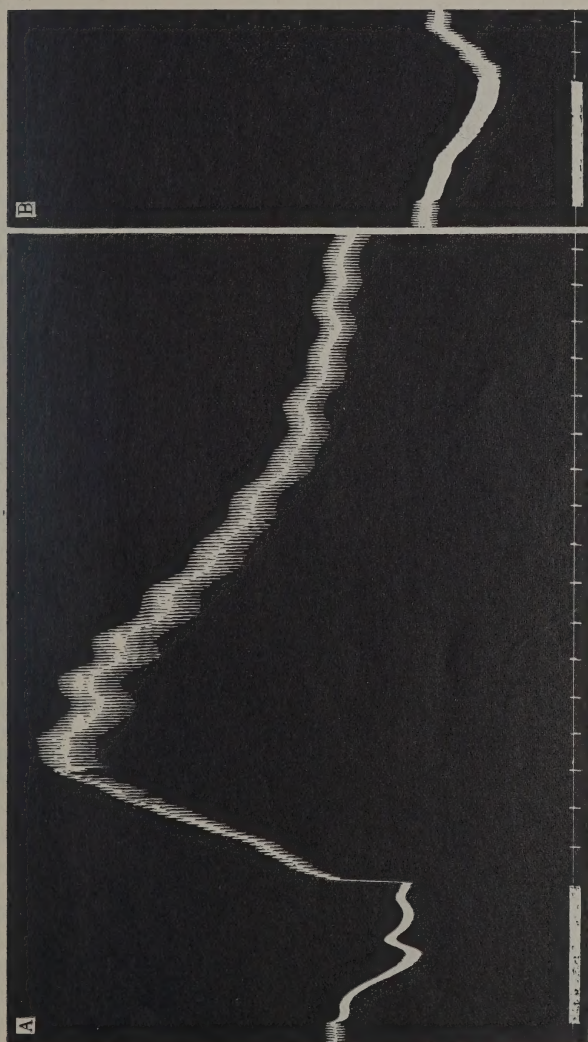


Fig. 3. Blood pressure record after tying the carotid, subclavian and iliac arteries and denervating the splanchnic area. Original size. Time intervals, 30 seconds.

A, Asphyxia 2 minutes. Rise of pressure at end of 1 minute and again after asphyxial period. (Adrenals then tied off).

B, Asphyxia 2 minutes. Both rises absent.

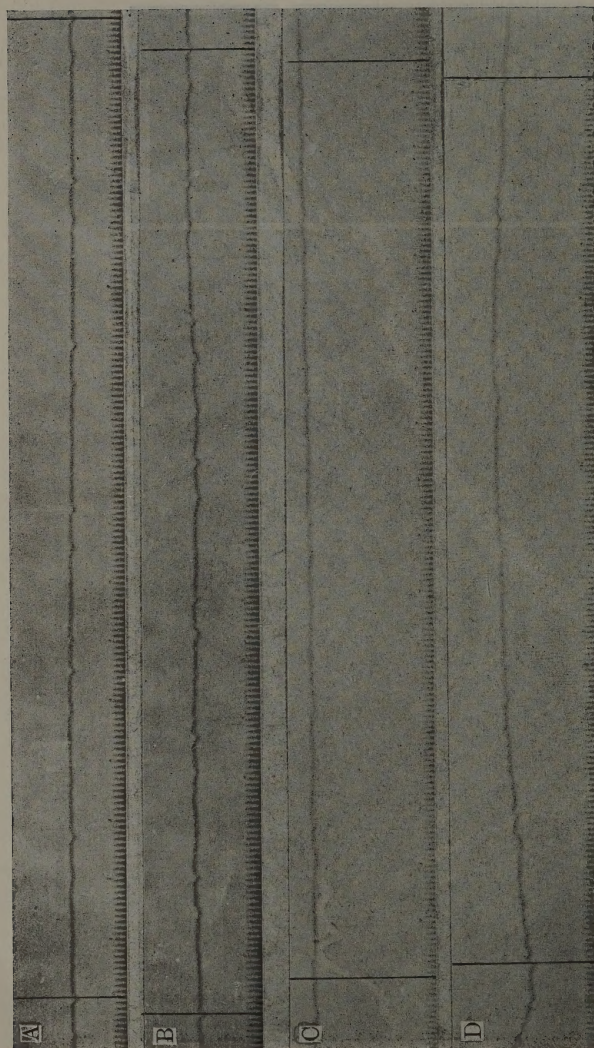


Fig. 4. Electrocardiograms of the denervated heart. Time intervals, 1/100 second. Above the time record the small dots mark 1/10 second.

A, Animal calm, heart rate 217 beats per minute. April 8.

B, Animal excited, heart rate 255 beats per minute. April 8. (Adrenal removal completed 9:50 a.m., April 10.)

C, Animal calm, heart rate 217 beats per minute. April 10, 2:40 p.m.

D, Animal excited, heart rate 221 beats per minute. April 10, 2:43 p.m.

under ether with aseptic precautions; later the right vagus nerve is severed below the recurrent laryngeal branch; and still later, the left vagus nerve is cut in the neck. The heart is thus wholly disconnected from the central nervous system and any agency causing an increase in the heart rate must exert its influence through the blood stream. In figure 4 are presented electrocardiographic records of the heart rate in a cat, operated upon as above described. The records show that with the adrenal glands normally innervated the rate was 217 per minute when the animal was calm, and 255 when excited. And after the adrenal glands were removed the rate when calm was 217 and when excited was 221.

The results obtained with the isolated heart used as an indicator of adrenal secretion thus confirm in every respect the results obtained eight years ago by the catheter method.

Care in assuring isolation of the adrenal glands. If the splanchnic nerves are severed or if the adrenal gland is removed on one side and the splanchnic fibers are cut on the other, as Stewart and Rogoff have noted, adrenal secretion may be isolated from nervous control in most cases, but there is not absolute certainty that this procedure will wholly eliminate nervous influences (29). For example, in one case, after the heart was wholly denervated, sciatic stimulation for one minute increased the rate from 220 to 264 beats per minute. The splanchnic nerves were then isolated in the thorax and cut. In two minutes the heart rate had dropped down to 192 beats per minute. Sciatic stimulation now increased the rate to 204, i.e., a rise of 12 beats per minute.

Similar observations have been made on animals with denervated heart that have been kept alive and observed under excitement. In one such case there was an increase of 42 beats per minute, although the left adrenal gland had been removed and the right splanchnic cut in the abdomen on the previous day. After removal of the right gland excitement had no effect. In another instance in which a similar operation had been performed there was an increase of approximately 28 beats a minute during excitement, an increase which disappeared as soon as the remaining adrenal gland was excised and the animal allowed to recover from etherization. It is possible, therefore, that other fibers than those contained in the splanchnic supply, or that occasionally, perhaps, a crossing of fibers from one splanchnic supply to the gland of the other side of the body, may be present in the cat and may thus lead to erroneous conclusions.

It has been assumed that by tying the adrenal veins at their junction with the inferior cava and the lumbar veins as they approach the adrenal glands, all possibility of an entrance of adrenal secretion into the blood stream has been excluded (10). That this may be a reasonable assumption in most cases was shown by Flint's studies of the blood supply of the cortex and medulla, which brought out the fact that the vessels of the two parts of the gland are separate. He reported, however, that as a variation from the usual condition, anastomosis may be present between the branches of the venous tree in the adrenal medulla and the venous plexus of the capsule (25). Under these circumstances the blood might flow from the medulla to the venous plexus which normally empties into the renal, phrenic and lumbar veins, into the *venae comites* of the suprarenal arteries, and to a less degree into the other veins. Further evidence of a direct vascular connection between the suprarenal gland and the veins of the kidney has been reported by Cow (26) who obtained an adrenal-like effect with blood taken from the kidney capsule of a cat.

In several instances in the course of the observations reported in this paper adrenal effects were seen after tying the lumbo-adrenal veins on both sides of the glands. In one case, after these veins had been thus tied, asphyxia caused the heart rate to increase from 166 to 206 beats a minute. The glands were then tied off completely, whereupon asphyxia had no effect (see table 2, February 17). In another instance, after the lumbo-adrenal veins had been carefully tied, injection of adrenalin into the vein as it crossed the gland caused a high rise of blood pressure, and in still another instance in which the veins were tied, splanchnic stimulation for 30 seconds caused the heart rate to rise from 172 to 248 beats per minute.

From these observations it is clear that conclusions based on results obtained when only the lumbo-adrenal veins are tied may lead to erroneous conclusions. The only absolutely safe method is that of excluding the glands from any possible action in the body by removing them or completely tying them off.

The gradual rise of pulse rate on repeated stimulation. A fact commonly noted in the course of the present experimentation was a gradual rise of the pulse rate with the lapse of time and with repeated indirect stimulation of the adrenal glands. In one instance an animal anesthetized with urethane had, after denervation of the heart, a pulse of 176 beats per minute. Repeated sciatic stimulation and asphyxia were accompanied by temporary increases of the pulse above the basal rate,

varying from 16 to 52 beats per minute. As these stimulations recurred, however, the basal rate gradually rose from 176 to 204. On tying off the adrenal glands completely, the rate fell to 152.

The increase of rate and its persistence at a progressively higher level with repeated stimulation are possibly facts of considerable importance in relation to the interaction of the endocrine glands, and deserve further examination.

A fall of pulse rate on sciatic stimulation. A curious fact noted in a number of instances after the abdomen had been opened was that sciatic stimulation, instead of causing an increase in the rate of the denervated heart, actually resulted in a slower beat. In one such case sciatic stimulation for 30 seconds reduced the rate from 216 to 212 beats per minute; subsequent stimulation for 45 seconds lowered it from 216 to 204, and still later from 236 to 216. In another instance sciatic stimulation lowered the rate from 216 to 212 and later from 232 to 212. No important changes of blood pressure preceded the altered rate. The significance of these effects is difficult to perceive. In the cases mentioned asphyxia caused a marked increase in the heart rate.

DEFENSE OF THE ISOLATED HEART AS AN INDICATOR OF ADRENAL SECRETION

In a recent paper on hyperglycemia, Stewart and Rogoff have incidentally offered four different arguments opposed to the conclusion that effects seen in the denervated heart are satisfactory proof of increased adrenal secretion (27). These arguments are as follows:

1. They state that there is nothing strange about an increase in the rate of the denervated heart when the central end of the sciatic or the peripheral end of the splanchnic nerve is stimulated—"it is obviously dependent upon the better blood flow through the coronary vessels." For evidence they cite Guthrie and Pike as having shown that in the perfused mammalian heart the rate could be made decidedly faster by raising the pressure of the perfusion fluid. In the experiments cited, however, Guthrie and Pike were using the *excised* heart; they definitely declare that the denervated heart *in situ* (the preparation described in this paper) does not follow the law of the excised heart as regards pressure changes. After complete denervation of the heart, they report, "there is either no change in the pulse rate (with variation of pressure), or an increase in rate with a fall in pressure, or a decrease in rate with rise in pressure." In so far as these observations testify that variations of arte-

rial pressure have *no effect* on the rate of the denervated heart, they are in accord with the earlier observations of Martin (28) and the more recent studies of Knowlton and Starling (29) who found that, between 20 and 200 mm. Hg., pressure changes did not change the rate. Frequently in the course of the work here reported arterial pressure has been raised 30 to 40 mm. Hg., after adrenal influence had been excluded, with no increase whatever in the rate of cardiac pulsation (*cf.* fig. 2). This concordant evidence wholly contradicts the first argument which Stewart and Rogoff have offered to account for the faster rate of the denervated heart when used as an indicator of adrenal secretion.

2. The second argument offered by them is that the rise of blood pressure, by increasing the rate of blood flow through the denervated heart or other organ, increases the amount of adrenin passing in unit time, and the sensitive denervated area responds to increase in the amount even if no change takes place in the rate of adrenal secretion. In presenting this argument the critics have not considered that with a rise of pressure the blood would pass more rapidly through the adrenal vessels (see p. 406); and therefore, on the basis of their own views of unvarying adrenal secretion, the higher the pressure the more diluted the adrenin—a condition which renders their argument unsound.

It is not necessary, however, to rely on argument. The simple experiment of preventing a rise of pressure may be tried. In figure 5 a record is presented of an increase in rate of the denervated heart from 144 to 180, i.e., a rise of 36 beats per minute, as a consequence of sciatic stimulation. The pressure rose about 58 mm. Hg. When the rate had fallen to 148 per minute the sciatic was again stimulated, but the pressure was prevented from rising by compression of the flexible thorax between the fingers and thumb. This is a procedure which, in the absence of the adrenal glands, is not attended by a faster beat of the denervated heart. The rate increased, however, from 148 to 184 beats per minute, a rise of 36 beats, as before. The more rapid rate developed during stimulation cannot be due to more adrenin contained in a larger volume-flow through the coronary arteries, for during stimulation the arterial pressure was not allowed to rise and augment the coronary flow. Furthermore, when the pressure was allowed to rise (50 mm.) the rapid rate, developed when the pressure was held down, did not become more rapid. The only explanation which affords a reasonable account of the faster rate is that there is something delivered to the heart through the blood stream which excites it to greater speed. Adrenin will do this. The fact that the faster rate disappears after

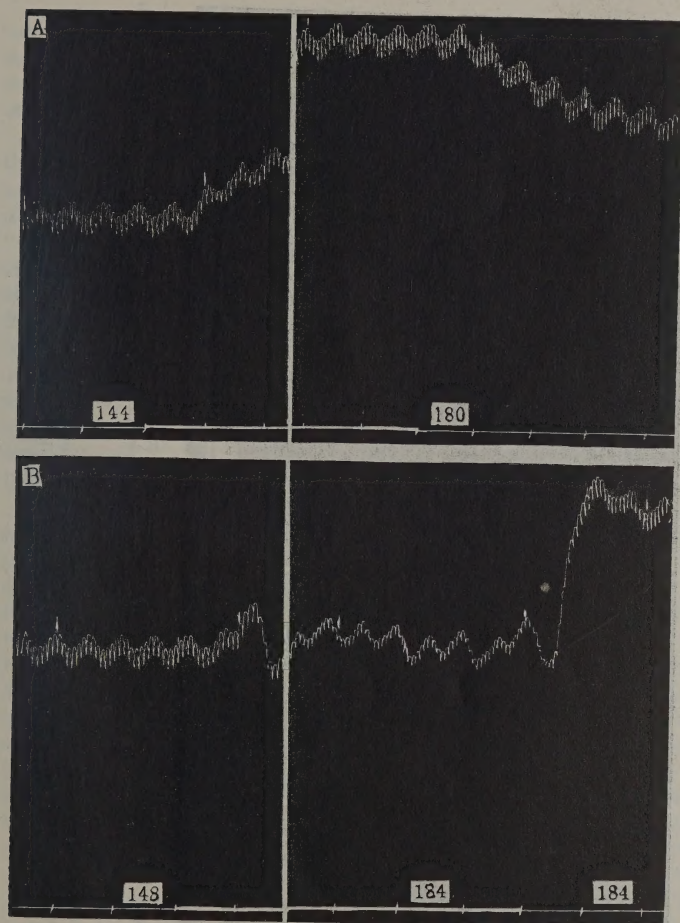


Fig. 5. Beginning and end of records of the beat of the denervated heart, mercury manometer. Original size. Time intervals, 5 seconds.

A, Sciatic stimulation 45 seconds, 1:01. Increase of rate from 144 to 180 per minute.

B, Sciatic stimulation 55 seconds (1:05). Increase of rate from 148 to 184 though pressure-rise checked by thoracic compression. No further increase with rise of pressure.

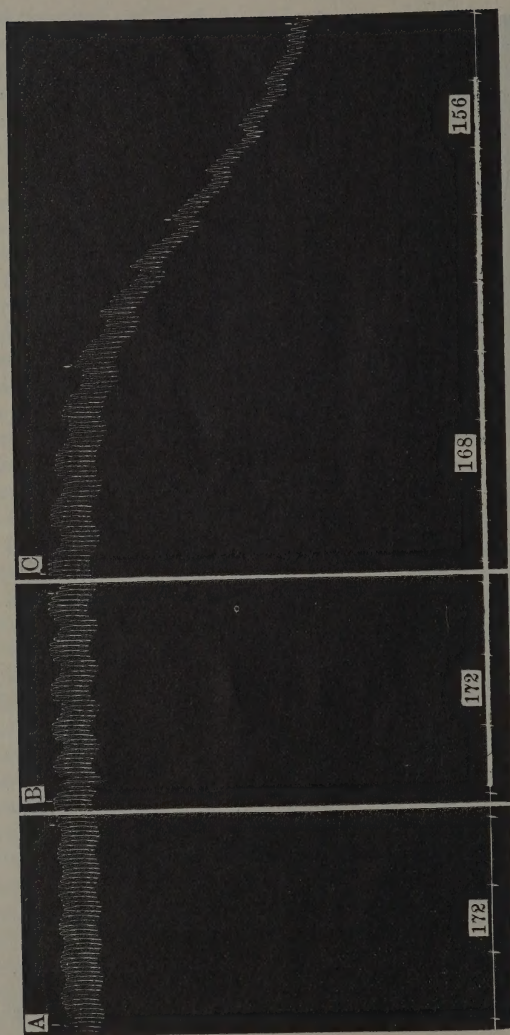


Fig. 6. Record of the beat of the denervated heart, (mercury manometer), after adrenalectomy and with a continuous uniform intravenous injection of adrenalin, 0.08 mgm. per minute. Heart rate thus increased from 132 to 172 beats per minute.

A, Time intervals, 5 seconds.

B, Beginning of 85 seconds of asphyxia. Heart rate 172 beats per minute.

C, End of 85 seconds of asphyxia. Heart rate before pressure fall, 168, later 156 beats per minute.

removal of the adrenal glands, although the rise of pressure still follows splanchnic stimulation (see fig. 1), is proof that this is the agent which is acting. Experimental test, therefore, denies the validity of Stewart and Rogoff's second argument.

3. Their third argument is directed against the use of any organ in the body as an indicator of adrenal secretion when asphyxia is employed as a stimulus, because asphyxia may be expected to alter the reactivity of the test object to adrenin, making it, for example, more sensitive. "We never supposed," they declare, "that it was possible to use in one observation an asphyxiated test object and in the comparison observation the same object with unobstructed respiration, or to assume that if there was any difference in reactions, it must be due to a difference in the rate of output of epinephrin; the condition of the test object itself being of no moment." Again this is argument and not experiment. Experiment has shown that increase of carbon dioxide causes a decrease, not an increase, in the rate of the denervated heart, and that nevertheless, adrenin, if superadded, produces a faster beat (30).

As shown in figure 6, when, after removal of the adrenal glands, adrenalin (1:200,000) is allowed to run (1 cc. in 15 seconds) steadily into a vein, asphyxia does not cause an increase of rate. The stream of adrenalin raised the rate from 132 to 172; after asphyxia had prevailed for 50 seconds the rate dropped to 168; and as the asphyxial state continued the rate became slower, dropping to 156 with a fall of pressure. A higher rate was possible, for the heart was obviously not beating at top speed, and yet there was no increase of rate at any stage in the development of asphyxia. Clearly the asphyxial condition did not render the test object more sensitive to the steady inflow of adrenalin. In the experiment illustrated in figure 2, an asphyxia lasting one minute caused an increase in the rate of the denervated heart of 32 beats a minute when the adrenal glands were connected with the circulation, but when these glands were completely tied off asphyxia for the same length of time caused no increase. The test object was in both cases subjected to identical periods of asphyxiation. Since asphyxia in the absence of the adrenal glands had no effect on the rate, whereas asphyxia with the adrenal glands present caused the characteristic acceleration which attends adrenal activity, the conclusion is warranted that the differential element in the complex, namely, the possibility of adrenal secretion, is the occasion for the typical adrenal effect. It should be remembered that Anrep (11) likewise obtained no effect of asphyxia alone,

i.e., no contraction of the denervated limb, in the absence of the adrenal glands; indeed, toward the end of the asphyxial period there was dilatation of the vessels ascribable to the direct action of the asphyxial blood on the vessel walls. This was in marked contrast to the asphyxial effect seen when the adrenal gland was present; then even a large rise of general arterial pressure, more than 50 mm. Hg., was insufficient to distend the vessels of the denervated limb, which were held contracted, according to Anrep's evidence, by secreted and circulating adrenin. Stewart and Rogoff's third argument, therefore, has no experimental warrant.

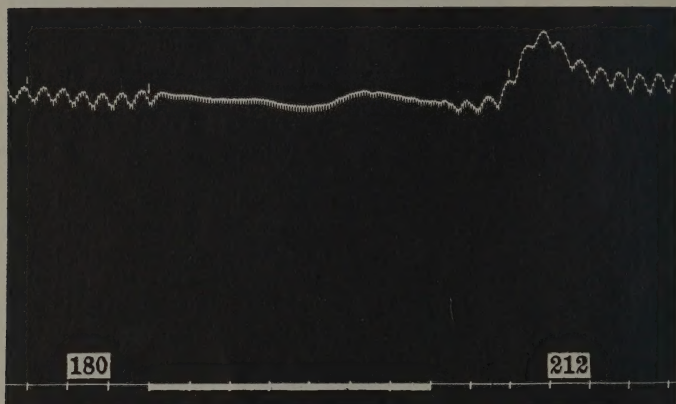


Fig. 7. Record of the beat of the denervated heart, (mercury manometer) in an animal with limb and carotid arteries tied and all mesenteric nerves severed. Enlarged one-sixth. Time intervals, 5 seconds.

Asphyxia for 35 seconds increased the heart rate from 180 to 212 beats per minute, with no noteworthy previous change in blood pressure.

4. Their fourth argument is that afferent stimulation by constricting the splanchnic vessels lessens the blood flow through the liver; in consequence the adrenal secretion contained in the cava blood is less diluted (i.e., more concentrated) than normal and therefore has more stimulating power. Again it is not necessary to rely on argument. In figure 7 is presented a record of the beats of a denervated heart in an animal in which all the nerves of the mesentery were entirely severed and the animal then asphyxiated. The rate before asphyxia was 180

beats per minute. This was increased by asphyxia 32 beats per minute. There is no possibility under these circumstances of any greater concentration of secreted adrenin because of failure of blood to pass through a constricted splanchnic area, for the nerves which would cause constriction of these vessels had been previously cut. Furthermore, the pressure did not fall, i.e., the flow was not made slower during the asphyxiated period. The effect must be ascribed to greater concentration of adrenin in blood delivered to the heart, due to an increased secretion of the adrenal medulla. The fourth argument, therefore, like the first three, fails to stand experimental test.

An observation having an important bearing on all four arguments and, indeed, on all conclusions arising from use of the "cava pocket" is that reported above (see p. 415) in giving evidence of adrenal activity at times of emotional excitement. As figure 4 shows, the rate of the denervated heart in an animal resting quietly with the adrenal glands intact was 217 beats a minute. When these glands were removed, *there was not at any time a reduction of the rate*. Recently Stewart and Rogoff (30) have testified that the "steady spontaneous discharge" from the adrenal glands in their experiments—an amount estimated as not more than 0.0002 mgm. per k. per minute—is sufficient to affect the heart. If with nerves intact there were in natural conditions the constant secretion which they declare to be "normal," removal of the glands should have been followed by a slower pulse. That the pulse did not fall below the "quiet" rate after adrenalectomy obviously permits the inference that in calm and peaceful existence there is no secretion from the adrenal glands sufficient to influence the response of an extremely sensitive indicator. In that case any attempt to explain the increased heart rate by greater delivery of adrenin or by greater concentration of it in the blood, due solely to shifts of the circulation, would be not at all pertinent.

The only factor which Knowlton and Starling found effective in causing prompt alteration of rate of the isolated heart was change of temperature. In order to increase the rate 40 beats per minute, however, the temperature of blood entering the heart had to be raised about 7°C. (29). It is inconceivable that the effects recorded above are due to the delivery of warmer blood to the heart.

From the foregoing facts the conclusion is warranted that the explanations offered by Stewart and Rogoff to account for adrenal effects on the basis of greater flow or altered distribution of the blood have no experimental support.

CRITICISM OF METHODS YIELDING NEGATIVE EVIDENCE

A review of the previous sections of this paper reveals unanimous agreement among investigators, with the exception of Stewart and Rogoff, that painful stimulation, asphyxia and emotional excitement evoke adrenal secretion. Nevertheless, the care with which Stewart and Rogoff conducted their experiments, the quantitative methods which they employed and the variety of their experiments have led to their results being given a considerable degree of credence. As previously stated, the discrepancy between their conclusions and those reached by all other investigators naturally raises the question as to whether some difference in the methods employed would not account for the difference in the results. Since Stewart and Rogoff are alone in their contentions, it is perhaps reasonable to inquire whether the peculiar method which they employed, rather than the various methods used by others, may not have features which would account for the discrepant results.

The method of Stewart and Rogoff. Stewart and Rogoff obtained evidence of adrenal secretion by the use of a "pocket" in the inferior vena cava (32). This pocket was made by clamping the vena cava immediately above the iliacs, then clamping the renal veins, emptying the cava segment by stripping it upwards, and placing a clamp on the vessel above the entrance of the lumbo-adrenal veins. Any small branches of the cava segment were tied. The pocket thus formed was allowed to fill with blood from the adrenal veins, and the blood was either allowed to pass into the general circulation by removal of the clamp on the inferior cava, or was withdrawn and tested outside the body on preparations of rabbit uterus and intestine. The arrangement was modified in the "permanent pocket" by tying splanchnic vessels and shutting off the blood flow in the hind quarters. Experiments performed under these conditions revealed a spontaneous liberation of adrenin.

In one of their early papers Stewart and Rogoff state (32) that they are "not able to decide definitely whether this liberation is a normal physiological process merely unveiled by the experiments, or an abnormal process dependent upon the necessary conditions of the observations,—anesthesia, unavoidable excitation of afferent nerves, etc." They mention, however, the relative constancy of the amount secreted as in favor of the former hypothesis. Later they suggest that the extensive operation required by their procedure may have produced so

great a spontaneous discharge that no detectable increase could be produced, and they admit that Tscheboksaroff's failure to obtain increased adrenal secretion on sensory stimulation may have been due to the severe operative procedure which he employed (33). This earlier caution regarding their method they seem to have gradually abandoned, for later they mention (7) the spontaneous secretion as being the "normal output of epinephrin" and state (34) that after section of the spinal cord the secretion has all the characters of "normal secretion," and they repeatedly allude (9) to the amounts of adrenin found in the pocket as being the normal amounts. In recent papers (27), (35) they refer to their results as constituting "a striking illustration of the fact dwelt upon in previous papers that the output of epinephrin is relatively stable and not easily influenced experimentally," and they speak of the secretion occurring at a relatively constant rate as the "naturally secreted epinephrin of the organism." Rogoff (36) goes so far as to declare "it has been established beyond doubt that the adrenal glands continuously secrete a certain normal amount of epinephrin."

Before this view can be admitted, the effect of opening the abdominal cavity, clamping off the inferior cava, and repeatedly manipulating the abdominal contents, either in pressing blood out of the inferior cava or withdrawing it by syringe, must be examined. Fully twenty years ago Bayliss and Starling called attention to the profound effect which opening the abdominal cavity has on the intestines in causing them to become absolutely motionless. Local stimulation then provokes no response or only local contraction. *If both splanchnic nerves are divided*, the intestines within a short time commence to contract rhythmically and show the usual local reflexes. In order to study intestinal movements with the abdomen opened, they had to section both splanchnic nerves, or destroy the spinal cord, or excise the abdominal ganglia. "These facts," they state (37), "suggest that in the intact animal, at any rate under the conditions of our experiment, tonic or reflex influences are continually descending the splanchnic nerves and inhibiting the activity of the intestines." The observations of Bayliss and Starling may be confirmed by any one who will study gastro-intestinal movements in the opened abdomen. Even if there is slight indication of activity at any time with the splanchnics intact, the least stimulation applied to the intestine, even a gentle handling of the gut, suffices to produce a reflex inhibition of its entire extent. These well-established facts make an interesting commentary on the use of the

cava pocket as a mode of obtaining evidence of "normal" or "natural" secretion. There is no doubt that secretion from the adrenal medulla is subject to impulses delivered by the splanchnic nerves, and there is no doubt that opening the abdominal cavity under anesthesia results in a discharge of impulses along these nerves. The adrenal glands, therefore, are continuously and abnormally stimulated if the abdomen is opened. The conclusion that must be drawn is that the pocket method is incapable of yielding any reliable evidence regarding the "normal" secretion of these glands.

The isolated heart yields pertinent testimony as to the discharge of impulses along splanchnic pathways under experimental conditions. An examination of the cases summarized in tables 1 and 2 reveals that, after section of the splanchnic nerves or exclusion of the adrenal glands, there is a drop in the heart rate—in some instances 40, 44 and even 48 beats per minute. The most reasonable explanation for this result is that in these experiments splanchnic impulses were continuously stimulating the glands to activity and thus making the heart beat faster than it otherwise would. Quite apart from these effects, evidence exists in the inhibitory influence of anesthesia on gastrointestinal movements that anesthesia alone can arouse splanchnic impulses (*cf.* also Elliott, *loc. cit.*). Thus the "steady spontaneous discharge" from the adrenal glands, described by Stewart and Rogoff as "normal," is confirmed and explained. But one needs only to compare the drop in heart rate after adrenalectomy in acute experimental conditions (see figs. 1 and 2) with the absence of a drop after adrenalectomy in the non-anesthetized animal (see fig. 4) to realize how abnormal is the so-called "normal" secretion which occurs during operation.

Stewart and Rogoff, after considering the possibility that their "extensive operation" may have caused so great a secretion of the adrenal glands that asphyxia, for example, could not evoke a detectable increase, became convinced that this suspicion was not well founded because they noted, on stimulating the cut splanchnic nerve directly, evidence of a decidedly greater rate of secretion (38). Obviously, when a nerve is cut and then stimulated, an unusual effect may be due to liberation of material accumulated during the inactivity which followed denervation. Furthermore, because direct stimulation of a nerve, or central excitation by strychnine, will produce certain results, that is not proof that reflex stimulation, done under anesthesia, should produce the same results. For example, there is a marked difference between the intensity of muscular response caused by direct stimulation of the

sciatic nerve and that which may be induced by reflex stimulation. Again, an abdominal operation which arouses continuous activity in the splanchnic nerves might readily interfere with splanchnic reflexes. One of the methods employed by Cannon for recording graphically the effect of secreted adrenin in the body was that of denervating the mesentery, as described above (see p. 410). This method required opening the abdomen. It yielded constant results so far as the belated influence of asphyxia was concerned, but was commonly disappointing as a means of demonstrating the early influence of asphyxia; *and in the entire series of cases with opened abdomen there was only one in which sensory stimulation caused any effect ascribable to adrenal secretion.* For example, in the first five cases of table 2, the abdomen had been opened, and in these instances, though asphyxia was effective, sciatic stimulation yielded no response whatever. From this evidence it is clear that, either because the opening of the abdomen produces a secretion unsurpassable by reflex stimulation, or because that operation abolishes abdominal reflexes, the influence of sensory stimulation on the adrenal glands is not manifested. There is little wonder, therefore, that Stewart and Rogoff, who alone have employed the pocket method, with its attendant severe abdominal operation and repeated manipulation of the abdominal contents, failed to obtain the positive results which have been obtained by all other observers.

The foregoing facts and considerations warrant the conclusion that although the work of Stewart and Rogoff was admirably quantitative in character, it was done under experimental conditions which could not afford information regarding the normal secretion of the adrenal glands or the natural conditions which affect that secretion. This conclusion applies to all inferences as to the nature of adrenal activity which they have based upon employment of the pocket method.

The method of Gley and Quinquaud. In the paper by Gley and Quinquaud previously mentioned (10), evidence is adduced to prove that adrenal secretion has nothing to do with the efficacy of sympathetic nervous impulses as they affect the smooth muscles of blood vessels, a conclusion well supported by the previous observations of Hoskins and McClure (39). Gley and Quinquaud removed blood from the inferior cava immediately above the opening of the subhepatic veins, and again from the right or left ventricle, in each case after splanchnic stimulation. The blood thus obtained was injected in 20 cc. amounts into other dogs weighing from 4 to nearly 10 kilos. Only the blood which was taken from directly above the opening of the

adrenal veins caused any rise of pressure in the dog injected. They conclude, therefore, that the adrenin present in adrenal blood after splanchnic stimulation is found neither in the blood of the vena cava above the subhepatic veins nor in the blood of the heart.

In drawing this conclusion Gley and Quinquaud seem to have disregarded the fact that they were, in the first place, taking only a small portion of the secreted adrenin, which had already been diluted by the blood of the donor, and were then injecting this small portion into the blood stream of another dog, where it would be diluted to a much greater degree.

Gley and Quinquaud declare categorically that secreted adrenin is not carried by the circulation to the organs on which it acts, and that, if present at all, it is present in a quantity altogether minimal and insufficient to exercise its action. This declaration again is made without due regard to evidence already in the literature. The observations on the denervated limb, on the denervated kidney, on the denervated salivary gland and on the denervated heart, quoted or described above, clearly demonstrate that adrenal secretion may be stimulated by painful impulses, by asphyxia and by emotional excitement, and that the substance secreted under these circumstances not only is carried to the structures on which it acts, but produces on these structures pronounced physiological effects. Until this evidence is definitely proved to be unworthy of acceptance, the conclusion which Gley and Quinquaud have drawn must be regarded as quite unjustified.

INTERPRETATION OF THE FUNCTION OF THE ADRENAL MEDULLA

With the disappearance of the view that the adrenal glands produce some substance which neutralizes toxic material developed in the body, there have been left two theories to account for the rôle played by the adrenal medulla in the bodily economy. These are the tonus theory and the emergency theory.

The tonus theory, which has been advocated in the past (40) and still receives attention, holds that the function of the secreted adrenin is to maintain the sympathetic endings in a state of responsiveness to nervous stimulation or in a condition of moderate activity or tone. This view has definitely lost ground in the course of relatively recent investigations. A number of investigators have called attention to the depressive effect of small doses of adrenalin (39), (41). If the smallest dose which will have any influence whatever on the blood

vessels induces relaxation of the vessels, it is difficult to understand how the function of the secreted adrenin could be that of maintaining a state of tonic contraction. Furthermore, as has been repeatedly noted (42), double adrenalectomy does not for some time cause the fall of arterial pressure which naturally would be expected if continued adrenin secretion were needed to keep the pressure up; and also stimulation of the splanchnic nerves induces the same rise of pressure after adrenalectomy as before (10). From these results the conclusion has been drawn by Hoskins and McClure and by Gley and Quinquaud that the tonus theory is without adequate experimental support.

The emergency theory was presented by Cannon on the basis of studies of adrenal secretion following stimulation of afferent nerves, asphyxia and emotional excitement. In the papers bearing upon this theory emphasis was repeatedly laid upon the association between adrenal activity and the activity of the sympathetic division of the autonomic system in such emergencies. Nowhere has the statement been made that secreted adrenin has a function separate from that of the nerve impulses, except to increase the irritability of fatigued muscles (3) and to speed the coagulation of the blood (4). The idea originally suggesting these studies on adrenal secretion was that changes in the viscera originally induced by nervous impulses might be continued by circulating adrenin (43, p. 40). No claim has ever been made that there is at any stage a primacy of adrenin in the production of physiological or psychological changes seen during strong emotion.

In spite of the foregoing facts authors have written as if Cannon had been attempting to support the idea that emotional experiences were dependent upon circulating adrenin. Thus Stewart and Rogoff report (32), as if the matter had been questioned, that all signs of fright can be elicited by administering morphine to a cat with one adrenal removed and the other denervated.⁶ Rogoff points out (36) that the secretion of sufficient adrenin to produce symptoms of fright would be impossible, again as if any claim had been made that these symptoms were due to secreted adrenin. Gley and Quinquaud declare that the

⁶ Stewart and Rogoff noted dilatation of the pupil of the "denervated eye" when animals became frightened, though one adrenal was removed and the nerves to the other sectioned. Cannon and de la Paz tried this method of testing for adrenal secretion but could not persuade themselves that an eye still innervated by the third cranial nerve was really "denervated" and interpreted the prompt dilatation of the pupil in a paroxysm of rage as due to central inhibition of the still active constrictor muscles (see Cannon: *Bodily Changes in Pain, Hunger, Fear and Rage*, New York, 1915, p. 35).

persistent irritability of the nerves after the adrenal glands have been removed is opposed to the explanation which Cannon has given to experiments on the adrenin origin of emotions (10). Indeed, Cannon has been definitely charged with assuming that the reaction to fear and other emotional states is dependent on hypersecretion of adrenin (44). Careful reading of his work gives no support for these interpretations.

The concept of an emotion may be expressed either in psychological terms of subjective experience or in physiological terms of bodily change. Cannon's observations lend no support to the idea that adrenal secretion is essential to the subjective experience of strong emotion. Adrenin has its effect peripherally, on outlying viscera. An assumption that subjective feeling depends on circulating adrenin involves, therefore, supporting the view that emotion as a psychological state is the consequence of visceral changes. Cannon has, in fact, definitely argued against this view (43, p. 275).

If the critics of the emergency theory conceive emotion as bodily change, they will find in Cannon's consideration of the interrelations of emotions the point emphasized that it is the *sympathetic division of the autonomic system* which is the primary agency in mobilizing the bodily forces in times of great fear or rage (43, p. 268). To assume that secreted adrenin is necessary for the changes which occur under such conditions implies an acceptance of the tonus theory. This view has not been held by Cannon and receives no support in any observation he has reported. The only suggestion which he has offered (43, p. 64) that might be construed into support of such a view is that adrenal secretion given forth into the blood stream during excitement is a substance capable of inducing or augmenting the nervous influences which bring about the very changes in the viscera that accompany excitement. Naturally, this suggestion should be considered in conjunction with others; e.g., "it is possible that disturbances in the realm of the sympathetic are automatically augmented and prolonged through chemical effects of the adrenal secretion" (43, p. 38), and "the changes originally induced in the digestive organs by nervous impulses might be continued by circulating adrenin" (43, p. 40). These suggestions imply coöperation of chemical and nervous factors, but not a dependence of the nervous factors on the chemical.

The possibility has been recognized (43, p. 65) that in times of emotional stress there may be coöperation of secreted adrenin with the products of other endocrine glands simultaneously excited, which might render the adrenin much more effective than it would be by itself.

This is a possibility which should be kept in mind in connection with the emergency theory of adrenal secretion. Until this possibility has been tested, however, there is no need of going further than the facts will warrant in appreciating the coöperative character of secreted adrenin and sympathetic nervous impulses.

Thus far no reliable evidence has been brought out by any investigator that there is any secretion whatever of the adrenal glands under quiet, peaceful conditions. Results reported in this paper present the first indication that under such conditions there is no adrenal secretion or a secretion so slight as not to affect the denervated heart, an extremely sensitive indicator. Stewart and Rogoff have shown that the cat and the dog will live normally for weeks with one adrenal excised and the other denervated, an operation which results in no demonstrable flow of adrenin from the adrenal vein (45). These observations prove that adrenal secretion is not a necessity, at least in times of serene existence. Adrenin is secreted, however, in times of great emotional stress and under circumstances which cause pain or asphyxia. As stated at the beginning, the function of the adrenal medulla is to be looked for under conditions which rouse it to action. Excitement, pain or asphyxia are, in natural existence, commonly associated with violent struggle for self-preservation. Under such circumstances, as has been emphasized in the presentation of the emergency theory, the operation of the sympathetic division of the autonomic system together with the aid which adrenin affords will muster the resources of the organism in such a way as to be of greatest service to such organs as are absolutely essential for combat, flight or pursuit. It appears, therefore, that the emergency theory of the adrenal medulla is the only one which thus far has any experimental support.

It is a pleasure to express my thanks to Mr. H. F. Pierce for help in the early experiments above reported, and to Dr. Alexander Forbes for making the electrocardiograms.

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